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WHAT'S NEW IN INTENSIVE CARE

Intracranial pressure toxicity: a matter of dose, not thresholds

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Intracranial pressure (ICP) management remains central to the care of patients with severe traumatic brain injury (TBI) [1] and aneurysmal subarachnoid haemorrhage (aSAH) [2]. Historically, treatment decisions have relied on universal thresholds, most commonly 20 or 22 mmHg, based on observational data linking these values with outcomes [3, 4]. Such threshold-based strategies, however, fail to reflect the true burden of intracranial hypertension and do not allow for individualized care.

The concept of ICP dose [5], also referred to as pressure–time dose (PTD), integrates both the intensity and duration of ICP elevations. It is defined as the area under the curve (AUC) of ICP values exceeding a given threshold over time, expressed in mmHg·h (Fig. 1). This metric distinguishes between a transient spike and a prolonged moderate elevation—events that may have very different physiological and clinical consequences. The American College of Surgeons Trauma Quality Improvement Program (ACS TQIP) recognized this in its 2024 Best Practice Guidelines, stating that "the ICP dose, reflecting both the magnitude and time of exposure to intracranial hypertension, might be more important than a fixed ICP treatment threshold." Importantly, higher ICP dose has been linked with worse outcomes across the entire Glasgow Outcome Scale spectrum [5], not just mortality.

Supporting evidence in TBI

As early as 1991, Marmarou emphasized that "it is not the absolute level of ICP that is critical, but the duration and magnitude of ICP elevation. A brief increase to high ICP may be less harmful than a prolonged period of moderately raised ICP" [6]. More than three decades later, multiple studies confirm that ICP dose is a more accurate predictor of outcome than static thresholds. Vik [5] showed that cumulative exposure above 20 mmHg was associated with increased six-month mortality in severe TBI, and that time spent above this threshold correlated with both unfavourable outcomes and radiologic severity.

Building on this, Güiza and colleagues [7] developed a methodology to visualize ICP dose as combinations of pressure and duration across the entire range of observed values. They demonstrated that even values as low as 15 mmHg may be harmful depending on their duration, while higher levels, such as 20–30 mmHg, may be tolerated briefly, depending on patient age and autoregulatory status. Donnelly [8], Åkerlund [9], and Kempen [10] further confirmed and expanded these findings in independent cohorts. Collectively, these studies highlight that secondary brain injury from raised ICP must be considered in the context of cerebrovascular reserve and patient-specific physiology.

Supporting evidence in aSAH

Beyond TBI, similar results have been observed in aneurysmal subarachnoid haemorrhage. Magni [11] applied the ICP dose model to aSAH patients, showing that moderate exposure was significantly associated with unfavourable 6 month outcomes, even when mean ICP remained within accepted ranges. Carra and colleagues [12] later visualized dose–outcome relationships using the Güiza methodology [7]. Interestingly, the ICP burden plots of aSAH patients resembled those of TBI patients with impaired autoregulation. Their analyses showed that cumulative dose predicted outcome more effectively than time above a fixed threshold, reinforcing the concept that ICP dose captures clinically relevant risk.

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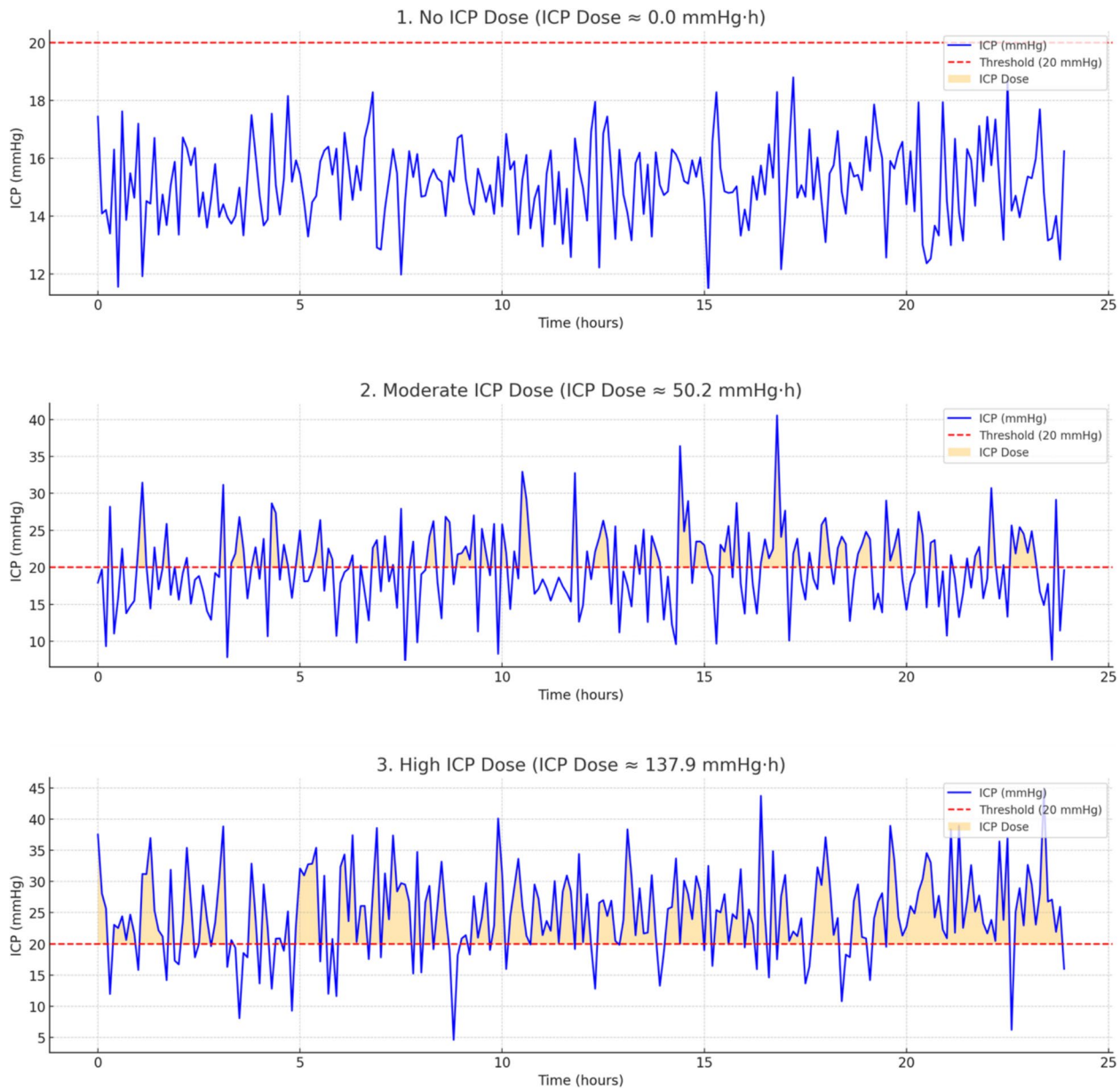
1. No ICP Dose (ICP Dose ≈ 0.0 mmHg·h)
2. Moderate ICP Dose (ICP Dose ≈ 50.2 mmHg·h)
3. High ICP Dose (ICP Dose ≈ 137.9 mmHg·h)
ICP (mmHg)
Threshold (20 mmHg)
ICP Dose
Time (hours)

Fig. 1 Concept of intracranial pressure (ICP) dose. ICP dose represents the cumulative exposure to intracranial pressure values exceeding a predefined threshold (here, 20 mmHg). The shaded area above the threshold indicates the total burden of elevated ICP over time. The three panels illustrate examples of no dose (0 mmHg·h), moderate dose (~ 50 mmHg·h), and high dose (~ 138 mmHg·h). Blue line: raw ICP signal; red dashed line: 20 mmHg threshold; shaded area: ICP dose. Mathematically, ICP dose can be expressed as: $ICP_{dose} = \int_{t_0}^{t_n} \max(0, ICP(t) - threshold)\, dt$ or in discrete form: $ICP_{dose} \approx \sum(ICP_i - threshold)$ For values above the threshold. This metric captures both the duration and intensity of intracranial hypertension, distinguishing transient peaks from prolonged moderate elevations

Alternative approaches, such as expressing ICP burden as the percentage of monitoring time above a given threshold [13, 14], provide robustness against variations in total recording time. However, they do not account for the intensity of ICP excursions. In practice, percentage time and mmHg·h may be viewed as complementary descriptors of intracranial hypertension.

Extensions to other monitoring metrics

The principle of dose can also be applied to other signals, including cerebral perfusion pressure, indices

of cerebrovascular autoregulation [15], brain tissue oxygenation [16], and lactate–pyruvate ratio [16]. This broader perspective emphasizes that cerebral tolerance to physiological insults is dose-dependent, multifactorial, and patient-specific.

Limitations and unresolved issues

Despite encouraging evidence, several limitations remain. Currently, ICP dose is mainly applied in research settings, though some recent devices integrate real-time dose calculation. Integration into multimodal platforms and predictive analytics is ongoing, suggesting that routine bedside use is feasible in the near future. However, major challenges remain, including the lack of consensus on thresholds and time windows for dose calculation, compounded by vendor-specific implementations that prevent standardisation. Harmonisation of definitions, technological integration, and prospective validation trials will be essential for clinical translation.

At present, the 20 mmHg threshold remains the most widely used threshold across multiple studies [5, 9, 11, 12] and is embedded in best-practice guidelines such as ACS TQIP 2024. However, ICP dose above this threshold may also reflect cases of refractory intracranial hypertension, who carry a poor prognosis independent of the metric itself. This bias should be recognised when interpreting dose–outcome associations. Moreover, ICP dose estimation is influenced by both timing of monitor placement and duration of observation. Delayed insertion may miss clinically relevant early intracranial hypertension, whereas very short recordings may underestimate the true cumulative burden. Future work should aim to define optimal and standardised time windows to ensure comparability across studies and feasibility for bedside application.

More critically, the ICP dose is inherently calculated in retrospect, and most data are from observational studies. Differences in patient populations (TBI vs aSAH) further complicate interpretation. Studies have used different baseline thresholds (15, 20, 22, or 25 mmHg) and variable time windows, and vendor- or software-specific implementations yield non-interchangeable metrics. These challenges underscore the urgent need for harmonized calculation standards.

Another critical limitation is the absence of prospective randomized controlled trials. As a result, its role in clinical practice remains exploratory. One of the most important implications relates to the timing of treatment escalation. The RESCUE-ICP trial [17], for example, considered decompressive craniectomy only after sustained ICP elevation despite maximal medical therapy, implicitly acknowledging the role of dose even if not labelled as such.

Two ongoing prospective trials (NCT04459806 and ISRCTN45963643) aim to prospectively validate and investigate the clinical implementation of ICP dose–guided therapy.

Future directions

Future research should focus on predictive, real-time applications. Recently, Carra [18] developed a machine learning model capable of predicting harmful ICP dose accumulation up to 30 min in advance with strong external validation performance. Such approaches pave the way for decision support systems that can anticipate risk and guide timely interventions. Among available approaches, the dynamic threshold methodology developed by Carra et al. [18] appears particularly promising, as it allows prediction of harmful ICP doses and is feasible for integration into advanced neurocritical care environments.

Equally important is the integration of ICP dose into multimodal monitoring platforms, allowing clinicians to interpret dose in the context of autoregulation, oxygenation, and metabolism. Ultimately, personalization of ICP dose thresholds according to age, autoregulatory capacity, and primary pathology may further refine its therapeutic value.

Conclusion

ICP dose represents an important evolution in neurocritical care. By capturing both the severity and duration of intracranial hypertension, it provides a physiologically meaningful and prognostically robust complement to static thresholds, offering additional prognostic granularity. Absolute ICP thresholds will continue to serve as essential treatment triggers, particularly in low-resource settings and during the acute phase when rapid bedside decisions are needed. While challenges remain in standardization, validation, and implementation, advances in artificial intelligence and multimodal monitoring hold promise for its translation into clinical practice.

The future of ICP monitoring is not *only* a number, it is also a dose; both remain essential for different purposes.

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Declarations

Conflicts of interest

Giuseppe Citerio reports receiving research grants from Neuroptics and Integra, as well as personal fees from both companies for consultancy and participation in lectures or educational events. Giorgia Carra and Geert Meyfroidt declare no commercial conflicts of interest. The views expressed are solely those of the authors. The ICMJE Disclosure Form has been completed.

Ethical approval

This article does not report on primary data collected from human participants. All data cited and discussed are derived from previously published studies with appropriate ethical approval. No new patient data were collected or analysed for this manuscript, and ethics approval was therefore not required.

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References

1. Hawryluk GWJ, Citerio G, Hutchinson P (2022) Intracranial pressure: current perspectives on physiology and monitoring. Intens Care Med 48:1471–1481. https://doi.org/10.1007/s00134-022-06786-y
2. Addis A, Baggiani M, Citerio G (2023) Intracranial pressure monitoring and management in aneurysmal subarachnoid hemorrhage. Neurocrit Care 39:59–69. https://doi.org/10.1007/s12028-023-01752-y
3. Wijdicks EFM (2022) 10 or 15 or 20 or 40 mmHg? What is increased intracranial pressure and who said so? Neurocritical Care. https://doi.org/10.1007/s12028-021-01438-3
4. Hawryluk GWJ, Rubiano AM, Totten AM (2020) Guidelines for the management of severe traumatic brain injury: 2020 update of the decompressive craniectomy recommendations. Neurosurgery 87:nyaa278. https://doi.org/10.1093/neuros/nyaa278
5. Vik A, Nag T, Fredriksli OA (2008) Relationship of 'dose' of intracranial hypertension to outcome in severe traumatic brain injury. J Neurosurg 109:678–684. https://doi.org/10.3171/jns/2008/109/10/0678
6. Marmarou A, Anderson RL, Ward JD (1991) Impact of ICP instability and hypotension on outcome in patients with severe head trauma. J Neurosurg 75:S59–S66. https://doi.org/10.3171/sup.1991.75.1s.0s59
7. Güiza F, Depreitere B, Piper I (2015) Visualizing the pressure and time burden of intracranial hypertension in adult and paediatric traumatic brain injury. Intensive Care Med 41:1067–1076. https://doi.org/10.1007/s00134-015-3806-1
8. Donnelly J, Güiza F, Depreitere B, Meyfroidt G, Czosnyka M, Smielewski P (2021) Visualising the pressure-time burden of elevated intracranial pressure after severe traumatic brain injury: a retrospective confirmatory study. Br J Anaesth 126(1):e15–e17. https://doi.org/10.1016/j.bja.2020.09.018
9. Åkerlund CA et al (2020) Impact of duration and magnitude of raised intracranial pressure on outcome after severe traumatic brain injury: a CENTER-TBI high-resolution group study. PLoS One 15(12):e0243427. https://doi.org/10.1371/journal.pone.0243427
10. Kempen B, Depreitere B, Piper I (2024) Visualization of the intracranial pressure and time burden in childhood brain trauma: what we have learned one decade on with KidsBrainIT. J Neurotrauma 41:e1651–e1659. https://doi.org/10.1089/neu.2023.0254
11. Magni F, Pozzi M, Rota M (2015) High-resolution intracranial pressure burden and outcome in subarachnoid hemorrhage. Stroke 46:2464–2469. https://doi.org/10.1161/strokeaha.115.010219
12. Carra G, Elli F, Ianosi B (2021) Association of dose of intracranial hypertension with outcome in subarachnoid hemorrhage. Neurocrit Care 34:722–730. https://doi.org/10.1007/s12028-021-01221-4
13. Svedung Wettervik T, Howells T, Hånell A, Nyberg C, Ronne-Engström E (2022) NT-proBNP and troponin I in high-grade aneurysmal subarachnoid hemorrhage: Relation to clinical course and outcome. J Crit Care 72:154123. https://doi.org/10.1016/j.jcrc.2022.154123
14. Hawryluk GWJ et al (2020) Analysis of normal high-frequency intracranial pressure values and treatment threshold in neurocritical care patients: insights into normal values and a potential treatment threshold. JAMA Neurol 77(9):1150. https://doi.org/10.1001/jamaneurol.2020.1310
15. Güiza F et al (2017) Cerebral Perfusion Pressure Insults and Associations with Outcome in Adult Traumatic Brain Injury. J Neurotrauma 34(16):2425–2431. https://doi.org/10.1089/neu.2016.4807
16. Gouvêa Bogossian E et al (2025) Visualizing the burden of brain tissue hypoxia and metabolic dysfunction assessed by multimodal neuromonitoring in subarachnoid hemorrhage patients: the TITAN study. Intensive Care Med 51(4):708–720. https://doi.org/10.1007/s00134-025-07888-z
17. Hutchinson PJ, Kolias AG, Timofeev IS (2016) Trial of decompressive craniectomy for traumatic intracranial hypertension. N Engl J Med 375:1119–1130. https://doi.org/10.1056/nejmoa1605215
18. Carra G, Güiza F, Piper I (2023) Development and external validation of a machine learning model for the early prediction of doses of harmful intracranial pressure in patients with severe traumatic brain injury. J Neurotrauma 40:514–522. https://doi.org/10.1089/neu.2022.0251